Appendix A

Relationship between Claims 204 and 205 and Claim 3 of the Krieg '646 Patent

Claim 204

"Method of treating an allergy in a vertebrate".

This is the preamble of Applicants' claim 204. Krieg claim 3 recites that the claimed method is for "desensitizing a subject against the occurrence of an allergic reaction in response to contact with a particular allergen". This in effect states that the method is directed to treatment of an allergy, which is recited in Applicants' claim 204. As is well known in the art, allergy treatment when using an antigen which causes the allergy, or an allergen,[3] involves administering the offending antigen in an effort to "desensitize" the subject or vertebrate so that reaction to subsequent exposure to (or contact with) the offending antigen is reduced ("against the occurrence of an allergic reaction in response to contact with a particular allergen"; claim 3 of the Krieg '646 patent). Applicants' specification refers to "conventional immunotherapy protocols" and desensitization obtained by administering protein antigen. Page 36, lines 1-4 and lines 10-13; *see also* Example VI. Example VII shows a reduction of antigen-specific, allergen-associated IgE production in mice receiving an antigen-encoding plasmid that also contains an immunostimulatory, CG-containing sequence.

Krieg's '646 patent specification refers to using immunostimulatory nucleic acid molecules in "desensitization *therapy* for allergies" and that "the instant claimed nucleic acid molecules can be administered in conjunction with a particular allergen to a subject as a type of desensitization *therapy* to *treat* or prevent the occurrence of an allergic reaction." Col. 34, lines 6-9; col. 6, lines 62-65 (emphasis added). The Krieg '646 patent specification also makes the connection between the observed shift toward a Th1 response effected by the CG-containing immunostimulatory nucleic acids and the allergy context:

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[3] This is in contrast to other allergy "treatments" which do not involve administration of the offending antigen, and are thus not based on immunotherapy. Examples of these other types of "treatments" include antihistamines.

"Based on the ability of the immunostimulatory nucleic acid molecules to shift the immune response in a subject from a Th2 (which is associated with production of IgE antibodies and allergy) to a Th1 response (which is protective against allergic reactions), an effective dose of an immunostimulatory nucleic acid (or a vector containing a nucleic acid) alone or in conjunction with an allergen can be administered to a subject to *treat* or prevent an allergy." Col. 34, lines 18-26 (emphasis added).

This connection between Th1 shift and applicability to therapy in the allergy context is mirrored in Applicants' specification. *See, for example*, page 49, lines 9-10 ("TH1 responses are to be of particular importance in the treatment of allergies and AIDS.") in conjunction with page 4, lines 9-11 ("The invention also includes naked gene expression vectors for use in manipulating cellular immune responses toward the TH1 compartment").

Both recitations aim for the same goal that is well recognized in the art: reduction of allergy-associated IgE antibodies, which mediate the unpleasant symptoms of allergy (such as histamine release, leading to runny eyes, itching, etc.). While Applicants' recitation is more concise than that of claim 3 of Krieg '646, both convey the same concept and objective via reduction of allergy-associated IgE production.

Claim 3 of the Krieg '646 patent recites that the recipient of the treatment is a "subject", which is defined in the specification as "a human or vertebrate animal. . .". Col. 13, lines 27-29. Applicants' claim 204 recites "vertebrate".

"An immunostimulatory nucleic acid in a plasmid, said immunostimulatory nucleic acid comprising 5'CG3' wherein C is unmethylated." Claim 3 of the Krieg '646 patent recites "an immunostimulatory nucleic acid, comprising: 5'X_1CG$X_2$3' wherein the immunostimulatory nucleic acid includes at least 8 nucleotides and . . .wherein X_1 and X_2 are nucleotides. . ." A plasmid is an obvious polynucleotide species in view of a polynucleotide of at least 8 nucleotides in length, and vice versa. In a plasmid, the recitation of X_1, X_2, etc. is rendered superfluous, as the CG sequence would *de facto* always be flanked by other nucleotides. The recitation of at

least 8 nucleotides is also rendered superfluous, as a plasmid must have at least 8 nucleotides. Conversely, a plasmid anticipates a polynucleotide of at least 8 nucleotides in length.

"Antigen which stimulates production of allergy-associated IgE antibodies in the vertebrate." Claim 3 of the Krieg '646 patent recites "allergen". One skilled in the art would readily recognize that an allergen is an antigen which stimulates an allergic response, and that an allergy in turn is an inappropriate immune response to the offending antigen. The *Academic Press Dictionary of Science and Technology* (1992) provides a standard dictionary definition of allergen ("an *antigen* that is capable of inducing an allergic reaction")(emphasis added) and an allergy ("an exaggerated physical response to some antigen. . . resulting when histamine or histamine-like substances are released from injured cells.").

It is also well known in the art that a hallmark of an allergic response is production of allergy-associated IgE antibodies in the subject having the allergic reaction. *Academic Press Dictionary of Science and Technology* (1992) provides a standard dictionary definition of IgE antibodies ("a class of immunoglobulins that are generally elicited by an allergen and that bind to the surfaces of mast cells"). Krieg's '646 specification states that allergies "are generally caused by IgE antibody generation". Col. 34, lines 7-9. Thus "allergen" and "an antigen which stimulates production of allergy-associated IgE antibodies" are essentially the same recitations.

"Wherein said antigen is encoded in the plasmid." Claim 3 of the Krieg '646 patent recites that an "allergen" is administered. Applicants' claim recites an obvious variation of administering the offending antigen, namely, that the antigen is encoded in the plasmid. Conversely, administering an antigen *per se* is obvious in view of administering an antigen which is encoded in a plasmid (polynucleotide). In terms of the role of antigen in modulating an immune response in the context of administering a CG-containing immunostimulatory sequence, an antigen-encoding sequence presents to the organism an antigen upon transcription and translation. One of ordinary skill would recognize that the delivery of an antigen encoded by a plasmid is an obvious alternative with respect to delivery of antigen *per se*. In terms of result, both an "antigen" and an "antigen encoded in a plasmid" stimulate an antigen-specific immune

response. Applicants also point out that claims of the Krieg '646 patent use these terms interchangeably. *See* claim 4 of the Krieg '646 patent, directed to methods of vaccination which recites administering "a vaccine antigen or an antigen encoded in a DNA vaccine". Other claims of the Krieg '646 patent use the term "antigen encoded in a DNA vaccine" as a species with respect to an "antigen". *See* claim 10 ("wherein the antigen is encoded in a DNA vaccine"; dependent from claim 6, which recites "an antigen"); claim 16 ("wherein the antigen is encoded in a DNA vaccine"; dependent from claim 14, which recites "an antigen"); claim 20 ("wherein the antigen is encoded in a DNA vaccine"; dependent form claim 18, which recites "an antigen"); claim 24 ("wherein the antigen is encoded in a DNA vaccine"; dependent from claim 22, which recites "an antigen").

The Krieg '646 patent specification equates the use of "antigen" and an "antigen encoded in a polynucleotide". The specification refers to the "antigen encoded by the [DNA] vaccine" as determining the specificity of the immune response, which is the same function that an antigen *per se* would serve in compositions containing immunostimulatory polynucleotides. Col. 33, lines 39-40. The Krieg '646 patent specification also describes expression vectors in the context of the invention and states that the invention includes expression vectors such as plasmids and "such other forms of expression vectors which serve equivalent functions [expression of an antigen] and which become known in the art subsequently hereto." Col. 13, lines 40-46. Original claim 18 (which is part of the specification) recites "[a]n improved method of vaccination in a subject, comprising administering to the subject a vaccine antigen or a nucleic acid encoding the vaccine antigen and a nucleic acid of claim 1."

If viewed as a species, an "antigen encoded by the plasmid" (a polynucleotide) anticipates the genus "antigen". Conversely, the species of "antigen encoded by the plasmid" (a polynucleotide) is an obvious species in view of the genus "antigen". Antigens encoded in DNA vaccines were known in the art as an immunogenic form of an antigen of interest. *See, for example, Nat. Medicine* (1995) 1:583-7 ("Preclinical Efficacy of a Prototype DNA Vaccine: Enhanced Protection Against Antigenic Drift in Influenza Virus") and *Ann. NY Acad. Sci.* (1995)

772:1-294 ("DNA Vaccines: A New Era in Vaccinology"). Thus, an "antigen encoded by a polynucleotide" and an "antigen" are obvious and/or anticipated in view of each other.

In addition, the Office has supported the species relationship of an "antigen encoded by a polynucleotide" and an "antigen" with regard to a generic claim reciting an "antigen." During previous prosecution of this application, a restriction requirement issued based on administration of antigen as a polypeptide and administration of antigen in the form of polynucleotide encoding the antigen and was withdrawn by the Office in favor of an election of species requirement. During an interview on November 28, 2000 with Applicants' representatives, the Examiners acknowledged that claims directed to the administration of antigen as a polypeptide and claims directed to administration of a polynucleotide encoding the antigen were species of a generic claim directed to administration of an antigen and were not subject to a restriction requirement. See Paper No. 19 (Interview Summary, mailed 12/05/00). The Office referred to administration of antigen in terms of both forms ("wherein the co-administering antigen is in the form of a polynucleotide"; "wherein the co-administering antigen is in the form of a polypeptide").

New claim 205

"Method for suppressing an allergic response to an antigen in a mammal susceptible to an allergic reaction to said antigen which stimulates production of allergy-associated IgE antibodies in the mammal". This is the preamble of Applicants' claim 205. Krieg claim 3 recites that the claimed method is for "desensitizing a subject against the occurrence of an allergic reaction in response to contact with a particular allergen". This in effect states that the method is directed to suppressing an allergic response to an antigen, which is recited in Applicants' claim 205. As is well known in the art in the context of allergy immunotherapy, treatment to suppress an allergic response which uses an antigen which causes the allergy, or an

allergen,[4] involves administering the offending antigen in an effort to "desensitize" the subject or mammal so that reaction to subsequent exposure to (or contact with) the offending antigen is reduced or suppressed ("against the occurrence of an allergic reaction in response to contact with a particular allergen"; claim 3 of the Krieg '646 patent). Applicants' specification refers to "conventional immunotherapy protocols" and desensitization obtained by administering protein antigen. Page 36, lines 1-4 and lines 10-13; *see also* Example VI. Example VII shows a reduction of antigen-specific, allergen-associated IgE production in mice receiving an antigen-encoding plasmid that also contains an immunostimulatory, CG-containing sequence.

Krieg's '646 patent specification refers to using immunostimulatory nucleic acid molecules in "desensitization therapy for allergies" and that "the instant claimed nucleic acid molecules can be administered in conjunction with a particular allergen to a subject as a type of desensitization therapy to treat or prevent the occurrence of an allergic reaction." Col. 34, lines 6-9; col. 6, lines 62-65. The Krieg '646 patent specification also makes the connection between the observed shift toward a Th1 response effected by the CG-containing immunostimulatory nucleic acids and the allergy context:

"Based on the ability of the immunostimulatory nucleic acid molecules to shift the immune response in a subject from a Th2 (which is associated with production of IgE antibodies and allergy) to a Th1 response (which is protective against allergic reactions), an effective dose of an immunostimulatory nucleic acid (or a vector containing a nucleic acid) alone or in conjunction with an allergen can be administered to a subject to treat or prevent an allergy." Col. 34, lines 18-26.

This connection between Th1 shift and applicability to suppressing an allergic response to an antigen is mirrored in Applicants' specification. *See, for example*, page 49, lines 9-10 ("TH1 responses are to be of particular importance in the treatment of allergies and AIDS.") in

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[4] This is in contrast to other allergy "treatments" which do not involve administration of the offending antigen, and are thus not based on immunotherapy. Examples of these other types of "treatments" include antihistamines.

conjunction with page 4, lines 9-11 ("The invention also includes naked gene expression vectors for use in manipulating cellular immune responses toward the TH1 compartment"). Also, see page 5, lines 13-15 ("The vectors are also of particular use in stimulating the TH1 compartment in preference to the TH2 compartment, thus suppressing IgE production is response to expressed antigen").

Both recitations aim for the same goal that is well recognized in the art: reduction of allergy-associated IgE antibodies, which mediate the unpleasant symptoms of allergy (such as histamine release, leading to runny eyes, itching, etc.). Both Applicants' recitation and that of claim 3 of Krieg '646 convey the same concept and objective via reduction of allergy-associated IgE production.

Claim 3 of the Krieg '646 patent recites "allergen". One skilled in the art would readily recognize that an allergen is an antigen which stimulates an allergic response, and that an allergy in turn is an inappropriate immune response to the offending antigen. The *Academic Press Dictionary of Science and Technology* (1992) provides a standard dictionary definition of allergen ("an *antigen* that is capable of inducing an allergic reaction")(emphasis added) and an allergy ("an exaggerated physical response to some antigen. . . resulting when histamine or histamine-like substances are released from injured cells.").

It is also well known in the art that a hallmark of an allergic response is production of allergy-associated IgE antibodies in the subject having the allergic reaction. *Academic Press Dictionary of Science and Technology* (1992) provides a standard dictionary definition of IgE antibodies ("a class of immunoglobulins that are generally elicited by an allergen and that bind to the surfaces of mast cells"). Krieg's '646 specification states that allergies "are generally caused by IgE antibody generation". Col. 34, lines 7-9. Thus "allergen" and "an antigen which stimulates production of allergy-associated IgE antibodies" are essentially the same recitations.

Claim 3 of the Krieg '646 patent recites that the recipient of the treatment is a "subject", which is defined in the specification as "a human or vertebrate animal. . .". Col. 13, lines 27-29.

Of the specific subjects listed in this recitation, 11 of the 12 are mammals. Applicants' claim 205 recites "mammal". Thus, "mammal" is an obvious variant of "subject."

"Parenterally administering to the mammal." The Krieg '646 patent describes various routes of administration including parenteral administration. *See, for example*, column 34, lines 46-55.

"An immunostimulatory nucleic acid in a plasmid, said immunostimulatory nucleic acid comprising 5'CG3' wherein C is unmethylated." Claim 3 of the Krieg '646 patent recites "an immunostimulatory nucleic acid, comprising: 5'$X_1CGX_2$3' wherein the immunostimulatory nucleic acid includes at least 8 nucleotides and . . .wherein X_1 and X_2 are nucleotides. . ." A plasmid is an obvious polynucleotide species in view of a polynucleotide of at least 8 nucleotides in length, and vice versa. In a plasmid, the recitation of X_1, X_2, etc. is rendered superfluous, as the CG sequence would *de facto* always be flanked by other nucleotides. The recitation of at least 8 nucleotides is also rendered superfluous, as a plasmid must have at least 8 nucleotides. Conversely, a plasmid anticipates a polynucleotide of at least 8 nucleotides in length.

"The antigen or the antigen encoded in the plasmid." Claim 3 of the Krieg '646 patent recites that an "allergen" is administered. Applicants' claim is written in the alternative and recites administration of the offending antigen or an obvious variation of administering the offending antigen, namely, that the antigen is encoded in the plasmid. Conversely, administering an antigen *per se* is obvious in view of administering an antigen which is encoded in a plasmid (polynucleotide). In terms of the role of antigen in modulating an immune response in the context of administering a CG-containing immunostimulatory sequence, an antigen-encoding sequence presents to the organism an antigen upon transcription and translation. One of ordinary skill would recognize that the delivery of an antigen encoded by a plasmid is an obvious alternative with respect to delivery of antigen *per se*. In terms of result, both an "antigen" and an "antigen encoded in a plasmid" stimulate an antigen-specific immune response. Applicants also point out that claims of the Krieg '646 patent use these terms interchangeably. *See* claim 4 of the Krieg '646 patent, which recites "a vaccine antigen or an antigen encoded in a DNA vaccine".

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